CASE REPORT

Recovery from pH 6.38: lactic acidosis complicated by hypothermia

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Survival after extreme arterial acidosis is uncommon. A case of metformin induced lactic acidosis is described where the presenting pH was 6.38 exacerbated by hypothermia (29°C). Increased anion gap acidosis, its varied aetiology, potential reversibility, and the role of hypothermia are discussed. Early liaison with a medical toxicology unit is recommended when this rare condition is suspected.

CASE REPORT

A 62 year old Hungarian born truck driver arrived at the emergency department having been phoned through as an "unconscious male". A few hours earlier his wife had put him to bed after he had complained of feeling "unwell". He was known to suffer from diabetes, which was diet and "tablet" controlled. There was no other relevant past medical history. The patient had been found in an unheated bedroom on a day where the ambient temperature was 13°C. His core body temperature was 29°C, respiratory rate 12/min, oxygen saturation 96%, blood pressure 115/64, heart rate 52/min and blood glucose reagent stix 12 mmol/l (Boehringer Mannheim). Further examination revealed no evidence of foetor (alcohol or acetone), head injury, neck stiffness, rash, murmurs, abdominal tenderness or masses. The patient was able to open his eyes to speech, utter incomprehensible sounds and flex to pain, (Glasgow Coma Score 9). Fundoscopy and pupillary examination were unremarkable. Tendon reflexes were symmetrically reduced with downgoing plantars. A 12 lead electrocardiogram showed a sinus bradycardia and chest radiograph was normal. Initial arterial blood gas (ABG) analysis revealed a profound uncompensated respiratory and metabolic acidosis with a pH of 6.38 (temperature corrected pH 6.49) and base deficit of 38. Initially, it was assumed that the extreme acidosis represented an error in analysis, however repeat ABG estimation using the intensive care unit's machine confirmed the extreme pH value (see fig 1).

A catheter specimen of urine was positive for glucose (++), protein (+), and blood (+), and negative for ketones. Serum osmolality was 322 mosm/kg, glucose 13.2 and lactate 24 mmol/l. Amylase, renal and liver profiles were normal. Computed tomography of the brain was normal and lumbar puncture also unremarkable. The patient was intubated and ventilated, following rapid sequence induction and transferred to the intensive care unit. In view of the profound increased anion gap acidosis of 35.2 mmol/l (normal anion gap 14 mmol/l, range 10–18 mmol/l) a toxicology screen was urgently requested. A full septic screen of urine, blood, sputum, nose, throat and cerebrospinal fluid revealed no growth. Reversal of the extreme acidosis and moderate hypothermia required mechanical ventilation, inotropic support, continuous intravenous bicarbonate therapy and passive external re-warming over a period of 12 hours. He received intensive care therapy for a further 10 days and was finally fit for discharge a month from admission. Toxicology later

confirmed the presence of almost twice the therapeutic plasma concentration of metformin (3.4 mg/l) and was negative for ketoacids, methanol/ethanol, fixed acids, paracetamol and salicylate. This result confirmed our suspicion of type B lactic acidosis secondary to metformin exacerbated by moderate hypothermia. His general practitioner confirms he has made a full functional recovery, 18 months after this episode although now retired and no longer prescribed metformin.

DISCUSSION

Both the resuscitation room (Chiron 860 series) and intensive care unit blood gas analyser (Chiron 865 series) had been "quality check assured" that day. The 800 series system blood gas analysers have a reporting range of 6.000 to 8.000 for temperature corrected arterial pH at a resolution of 0.001 (temperature range: 10.0–43.9°C). At a pH level of 6.5 the Chiron series ABG analysers have a precision of ± 0.002 pH units (1 standard deviation).¹ The agreement between the two machines makes the finding unlikely to be an erroneous result.

Metabolic acidoses with a high anion gap are attributable to the ingestion or endogenous generation of acids. The principal causes are ketoacidosis (3-OH butyrate, acetoacetate, lactate), lactic acidosis (lactate), uraemic acidosis (phosphate, sulphate) and poisoning by salicylates (salicylate lactate, lactate). Many definitions of lactic acidosis exist, however a working definition is a persistently raised blood lactate concentration together with a lowered blood pH. The acidosis is seldom significant unless blood lactate exceeds 5 mmol/l. Cases of lactic acidosis fall into two groups: type A and type B. The former is more common, and occurs in patients with signs of poor tissue perfusion with or without hypoxia. Type B lactic acidosis occurs as a result of administration of certain drugs, chemicals and toxic compounds, or as a result of an inherited metabolic defect that results in lactate accumulation.² Almost all cases of type B lactic acidosis are attributable to toxicological causes (biguanide, alcohol or salicylate associated) and metabolic causes are rare being the subject of single case reports.² Patients with severe type B lactic acidosis commonly show signs of shock and tissue hypoxia as a secondary and late event, and the distinction between type A and B lactic acidosis becomes less important once a working diagnosis has been established. The anion gap and plasma lactate concentration then become useful in following the progress of treatment.

Biguanides exert their glucose lowering activity mainly by inhibiting gluconeogenesis and reducing intestinal glucose absorption. This may result in an increase of gluconeogenic precursors namely lactate and pyruvate. The clinical picture of a severe metabolic acidosis without ketosis in biguanide treated diabetics was described as early as 1959³ and in 1982 phenformin was withdrawn from the UK market because of its higher risk of inducing lactic acidosis. It is still not known exactly which people are susceptible to metformin induced lactic acidosis, however factors that may potentiate the lacticidaemic effect are strenuous exercise, alcohol, renal

PATIENT SAMPLE REPORT			09 FEB 1999 16:16			PATIENT SAMPLE REPORT			09 FEB 1999 20:23		
SYSTEM 845 – 02898			Analysis Date 09 FEB 1999			SYSTEM 865 – 02773			Analysis Date 09 FEB 1999		
			Analysis Time 16:14						Analysis Time 20:22		
Sequence no 9640			Draw Date			Sequence no 31657			Draw Date		
Accession no			Draw Time			Accession no			Draw Time		
Source			Operator ID			Source			Operator ID		
Patient ID			Sex			Patient ID 123456–			Sex		
Birthdate			Physician ID			Birthdate			Physician ID		
Age			Location			Age			Location		
SYRINGE SAMPLE						SYRINGE SAMPLE					
ACID/BASE 37°C		Units	Reference Range			ACID/BASE 37°C		Units	Reference Range		
pH	6.389↓		(7.350–7.450)			pH	6.647↓		(7.350–7.450)		
pCO2	11.98↑	kPa	(4.67–6.00)			pCO2	3.75↓	kPa	(4.67–6.00)		
pO2	39.75↑	kPa	(10.00–13.33)			pO2	18.17↑	kPa	(10.00–13.33)		
HCO3 – std	1.9	mmol/L				HCO3 – std	2.7	mmol/L			
BEvt	–38.2	mmol/L				BEvt	–33.8	mmol/L			
OXYGEN STATUS 37°C						OXYGEN STATUS 37°C					
iHb	13.9	g/dL	(12.0–18.0)			iHb	12.3	g/dL	(12.0–18.0)		
pO2	39.75↑	kPa	(10.0–13.33)			Hct	36	%			
O2SAT	98.0	%				O2CT	16.3	mL/dL			
O2HB	97.0	%	(94.0–97.0)			pO2	18.17↑	kPa	(10.0–13.3)		
COHB	0.3	%	(0.0–1.5)			O2SAT	93.0	%			
MetHb	1.2	%	(0.0–1.5)			O2Hb	94.8	%	(94.0–97.0)		
HHb	1.5	%	(0.0–5.0)			COHb	0.3	%	(0.0–1.5)		
↑ or ↓ = exceeds reference range						MetHb 1.4 % (0.0–1.5)					
						HHb 1.5 % (0.0–5.0)					
CNICNCU						ELECTROLYTES					
Temp	29.0	°C				Na+	135.3	mmol/L	(135.0–148.0)		
FIO2	100.0	%				K+	3.59	mmol/L	(3.50–5.30)		
↑ or ↓ = exceeds reference range						Cl– 101 mmol/L (98–106)					
						METABOLITES					
						Glucose 19.31↑ mmol/L (3.7–5.2)					
						Lactate 18.56↑ mmol/L (0.50–2.00)					
						↑ or ↓ = exceeds reference range					

Figure 1 (left) Emergency department arterial blood gas sample on arrival (temperature corrected pH 6.494) and (right) ITU arterial blood gas sample after intensive care (uncorrected for temperature).

impairment, liver and cardiovascular disease. In cases of metformin induced lactic acidosis a pH of <6.9 with a raised urea and lactate greater than 18 mmol/l is associated with a poor outcome. There is no clear relation between age, sex, dose and duration of treatment and development of lactic acidosis.⁴ Therapeutic plasma concentrations are between 1–2 mg/l, but level monitoring has little clinical value, except when lactic acidosis is suspected or present as there is an association between high plasma metformin concentration and lactic acidosis. There is no correlation between plasma lactate and metformin concentration at therapeutic drug levels. The mean plasma elimination half life ranges from 1.5 to 4.5 hours and is prolonged in patients with renal impairment being closely correlated to creatinine clearance.⁵ It is unlikely hypothermia in itself affected renal clearance of the drug in our patient in the absence of shock and pre-existing renal impairment. We postulate therefore, that the metformin levels were raised in our patient because of excessive ingestion while in a confused state. The reported rate of confirmed metformin induced lactic acidosis is 5 cases per 100 000.⁶

Overall the prognosis of severe lactic acidosis is poor, mortality being very high in type A cases where survival is clearly related to the blood lactate concentration on presentation. A blood lactate in excess of 9 mmol/l is accompanied by a mortality rate of 80% or greater in type A lactic acidosis.⁷ Survival following extreme arterial pH values are well documented. A 24 year old man survived a near drowning episode

with cardiorespiratory arrest, hypothermia and a temperature (33°C) uncorrected arterial pH of 6.33.⁸ The lowest recorded arterial pH survived is 6.30 occurring in an 84 year old man after metformin ingestion, although further details are unavailable.⁹ Our case is unusual in that hypothermia and a reversible cause of acidosis were present. These three cases suggest extreme acidosis is a poor independent factor for survival if hypothermia or metformin induced acidosis, or both, are present.

Vasodilatation secondary to hypercapnoea, heat loss from radiation and confusion preventing him from putting clothes on in an unheated room may all have contributed to him becoming cold. Moderately severe hypothermia offers a cerebral protective role in situations of cardiorespiratory arrest principally by reducing cerebral metabolic rate and hence oxygen demand. The mechanism by which hypothermia may be protective after return of spontaneous circulation is unclear, however reduced susceptibility to oxidant injury has been proposed.¹⁰ It could be postulated, by a similar mechanism our patient was less susceptible to oxidant injury during acidosis correction in the presence of hypothermia.

In conclusion, after ketoacidosis, hyperosmolar non-ketotic coma, cerebrovascular accident and sepsis our case illustrates a less commonly encountered life threatening hazard to the diabetic patient. Early recognition of metformin induced lactic acidosis may permit a more proactive approach to care. Profound severe metabolic acidosis in the absence of hypoxia

should raise the suspicion of type B, potentially reversible lactic acidosis, and the need for discussion with a medical toxicology unit, for both advise and specialist drug assay. Hypothermia is known to increase cerebral tolerance to hypoxia, however it may also offer a protective role in severe acidosis. This case shows that extreme acidosis in the presence of hypothermia may respond to treatment and that a full recovery is possible.

Contributors

S Ahmad initiated the original idea, carried out the literature search and wrote the paper. M Beckett wrote and edited the paper. S Ahmad acts as guarantor.

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